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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/058,291	01/30/2002	James L. Hartley	0942.2850001/RWE/BJD	3302

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EXAMINER	
GUIDRY, GUY L	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,291	HARTLEY ET AL.	
	Examiner	Art Unit	
	Guy Guidry, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,36,38-54,58-66,69-75,77,79-88,90-93 and 95-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-36, 38-54, 58-66, 69-75, 77, 79-88, 90-93 and 95-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/20/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Furthermore, receipt is acknowledged of a declaration filed 20 June 2006. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action mailed 21 October 2005 has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 20 June 2006 has been entered. No claims are currently amended. Claims 1-34, 37, 55-57, 67-68, 76, 78, 89 and 94 are canceled. Claims 35-36, 38-54, 58-66, 69-75, 77, 79-88, 90-93 and 95-112 are pending in this application and under consideration in this Action. All objections/rejections not repeated herein are hereby withdrawn. Where applicable a response to Applicant's arguments is set forth immediately following the body of the any objection/rejection set forth herein. This action is Non-Final.

Information Disclosure Statement

With respect to the Information Disclosure Statements filed in this application, including the IDS filed 06/20/2006, it is desirable to avoid the submission of long lists of documents if it can be avoided. Eliminate clearly irrelevant and marginally pertinent cumulative information. If a long list is submitted, highlight those documents which have been specifically brought to applicant's attention and/or are known to be of most significance. MPEP § 2004. 13.; *See Penn Yan Boats, Inc. v. Sea Lark Boats, Inc.*, 359 F. Supp. 948, 175 USPQ 260 (S.D. Fla. 1972), aff 'd, 479 F.2d 1338, 178 USPQ

577 (5th Cir. 1973), cert. denied, 414 U.S. 874 (1974). *But cf. Molins PLC v. Textron Inc.*, 48 F.3d 1172, 33 USPQ2d 1823 (Fed. Cir. 1995).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 35-36, 35-49, 69, 72, 75, 79-82, 97, 99, 101-102, 107-108 and 110-112 stand rejected under 35 U.S.C. 102(b) as being anticipated by Fukushige et al. (of record).

This rejection is of record.

To summarize the salient aspect of the rejection, the limitation "immediately adjacent" is interpreted to mean one structure is next to another structure (e.g., instant Drawings, 4C); the limitation is not interpreted to mean that there are not intervening sequences between depicted structures. In addition, the limitation "first" and "second portion" of an antibiotic resistance gene are interpreted as broadly as reasonable to include a promoter as representing a one portion and driving transcription of a an antibiotic gene (i.e., second portion).

The crux of Applicant's argument is that the nucleic acid molecule represented in FIG. 2 of Fukushige clearly has intervening nucleotides between the CMV promoter and the *loxP* site. Applicant argues that the Office's interpretation of the claim limitation "immediately adjacent" is inconsistent with the interpretation that the ordinarily skilled artisan would give to that term in light of the present specification. That is, Applicant argues, the phrase "immediately adjacent" is interpreted to mean, in all instances, two defined sequences (sequence structures) without any intervening sequence between the two.

Applicant further argues that Figure 4C depicts an Sp6 promoter located "immediately adjacent" to a loxP site, but that the CMV promoter referred to by the Office is not immediately adjacent to the loxP site, as there are clearly intervening nucleotides between the CMV promoter and the loxP site (e.g., the entire SP6 promoter).

Response to arguments

Applicant's arguments filed 20 June 2006 have been fully considered but they are not persuasive.

As noted in the previous Office Action, the terms "adjacent" and "immediately adjacent" are not explicitly defined in the disclosure. The phrase "immediately adjacent" does not appear in the specification; the term "adjacent" appears twice. The first appearance occurs under the section titled "Definitions" (p. 12) in a definition of the term "Promoter" (p. 13, ll. 22-28) as follows "Promoter: is a DNA sequence generally

described as the 5'-region of a gene, located proximal to the start codon. The transcription of an adjacent DNA segment is initiated at the promoter region".

The second appearance of the term "adjacent" occurs in the section titled "Example 3: Subcloned DNA Segments Flanked by *attB* Sites Without Stop Codons, Part I: Background" in a description of the schematic on p. 38, ll. 4-10, which, as Applicant points out, represents the nucleotide regions that participate in an *att* recombination reaction in *E. coli* and wherein, Applicant argues, that by studying the diagram the artisan would deduce that the term "adjacent" used in this context means no intervening sequence between 2 defined sequences or structures.

Thus, in attempting to interpret the claim limitation "immediately adjacent", a person of skill would look to the term "adjacent" in the two instances described above and sensibly focus on the description in the specification that most closely parallels the limitations in the claims. As the claim limitation are drawn to recombination sites immediately adjacent to a promoter, given the choice of the two instances in which the term "adjacent" is used in the specification the artisan would reasonably find the meaning of "adjacent" as it applies to promoter in the definition given under the section "Definitions" as the most cogent to the claim limitations.

The ordinary artisan would be well aware that promoters are typically separated by intervening sequence from sequence for which the promoter promotes transcription. Considering the full disclosure, the occurrence of the word "adjacent" in the definition of "promoter" and in the description of the p. 38 diagram, and what is known to the ordinary artisan, one would logically conclude that "immediately adjacent" may

reasonably be interpreted to encompass two structures in proximity or in functional linkage either with or without the inclusion some amount of intervening sequence. There appears no logical reason to hold one interpretation over the other; the artisan would consider both instances wherein "adjacent" is used in the specification, leading to the conclusion that "immediately adjacent" may mean the inclusion or the exclusion of intervening sequence and Office personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. *In re Morris,* 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). The Office finds no evidence to support Applicant's argument that an exclusionary definition of the phrase "immediately adjacent" is to be found in or derived from a reading of the specification.

Further, the Office finds that the description cite by Applicant in this instance is Applicant's description of the prior art, not a description of limitations of the instant claims and therefore the descriptive use of the term "adjacent" is non-controlling with respect to meaning of the word in the instant claims.

The Office maintains that one of ordinary skill in the art will recognize that when read in the context of an expression vector a reasonable interpretation of the term "immediately adjacent" is that one functional element is *next to* another functional element. In other words, absent an exclusive definition for the term "immediately adjacent", the artisan would not interpret the term to mean that not a single nucleotide is present as between two functional elements on an expression vector/nucleic acid molecule. The drawings on which Applicant relies cannot be reasonably interpreted to support the exclusive definition argued by Applicant (e.g., Figures 4C, 8B, 8I and 8J). In

fact, as an exemplary schematic, Fig. 8I teaches that either *att*B1 or *att*B2 are immediately adjacent to GST and CAT genes respectively.

In examining the schematic of Fig 4C, there is no reason for interpreting the limitation "immediately adjacent" to mean that there is not a single nucleotide(s) between the claimed functional structures (e.g., CMV promoter and *loxP* site). Indeed, in observing the drawings, the claims and the disclosure on whole, and absent a definition to the contrary, the artisan would reasonably interpret the term "immediately adjacent" to mean two functional structures present next to each other without additional intervening functional structures. As such, Fukushige anticipates the rejected claims thus this rejection is maintained.

Claims 39, 43, 47-49, 79, 81 and 101-102 stand rejected under 35 U.S.C. 102(e) as being anticipated by Wahl et al. (of record, hereinafter the '177 patent).

This rejection is of record. The claims are interpreted consonant with what is stated above. Applicant argues that Wahl does not disclose a nucleic acid molecule comprising a promoter operably linked to an antibiotic resistance gene, and separated by a site-specific recombination site, wherein the promoter is also immediately adjacent to the site-specific recombination site because Wahl discloses some intervening sequence between the two structures.

Response to Arguments

Applicant's arguments filed 20 June 2006 have been fully considered but they are not persuasive. Effectually, Applicant's arguments are based on the interpretation of the limitation "immediately adjacent" as discussed in the preceding rejection.

As discussed above, the limitation "immediately adjacent" is not interpreted to mean that as between to functional elements on a nucleic acid molecule/expression construct there can be an intervening nucleotide(s). The '177 patent teaches a nucleic acid molecule where a promoter and an antibiotic resistance gene are next to a site-specific recombination site. Thus for the reasons of record and stated hereinabove, the '177 anticipates the rejected claims.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35-36, 38-51, 65-66, 69-75, 79-86, 92-93, 95-103 and 107-112 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fukushige et al. and Wahl et al. (hereinafter the '177 patent), and further in view of Lenski et al. (all of record).

This rejection is of record. The claims are interpreted consonant with what is stated above. In addition, the teachings of Fukushige and the '177 patent are incorporated and applied herein consonant with what is stated above. Additional embodiments are directed to the antibiotic resistance gene as being chloramphenicol and the host cell as bacterial, i.e., *E. coli*.

Applicant argues, Fukushige and Wahl are deficient as primary references on which to base a prima facie case of obviousness, as allegedly neither reference discloses a nucleic acid molecule comprising a promoter immediately adjacent to a site-specific recombination site that separates the promoter from an antibiotic resistance genes. Applicants argue that while it may disclose the use of a chloramphenicol antibiotic resistance gene in combination with E. coli cells, Lenski does not disclose nucleic acid molecules comprising a promoter immediately adjacent to a site-specific recombination site. Hence, Lenski does not cure the deficiencies in Fukushige and Wahl, and therefore cannot provide support for a case of obviousness.

Response to Arguments

Applicant's arguments filed 20 June 2006 have been fully considered but they are not persuasive. Applicant asserts that the Fukushige reference and the '177 patent are deficient as primary references because they fail to meet the limitation "immediately adjacent". Whether the primary references are deficient centers on the interpretation of the limitation "immediately adjacent". Reiterating what is already stated above, the limitation "immediately adjacent" is not interpreted to mean that there cannot be any nucleotide(s) between the functional elements of the claimed nucleic acid molecules. Therefore, since the primary references teach promoter elements and antibiotic resistance genes that are *immediately adjacent* to a site-specific recombination site, and when combined with Lenski et al. meet the limitations for a chloramphenicol antibiotic resistance gene and *E. coli* host cells. The rejection is still considered proper and is maintained.

Claims 35-36, 38-54, 58-66, 69-75, 77, 79-88, 90-93 and 95-112 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fukushige et al., Wahl et al., Lenski et al., and further in view of Griffiths et al. (all of record).

This rejection is of record. The teachings of Fukushige, Lenski and the '177 patent are incorporated and applied herein, consonant with the interpretations stated above. Additional embodiments are directed to the site-specific recombination site(s) as delimited to a lambdoid *att* site or mutants thereof. (i.e., claims 52-54, 58-64, 87-88, 90-91, 104-106). The additional claims are essentially directed to the same nucleic acid

molecules and host cells comprising the nucleic acid molecules, and only differ in the site-specific recombination system that is being claimed. Griffiths et al. explicitly discuss both the *lox* and *att* systems in the context of site-specific recombination as interchangeable equivalents. (e.g., col. 19; especially ll. 19-48). As such, it would have been obvious to modify the expression vectors taught by Fukushige or the '177 patent, as utilized in host cells. One would have been motivated to make such a modification to obtain the benefit of extending the range of site-specific recombination systems (recombinases and their cognate substrate/recognition sites).

Applicants specifically traverse the motivation to combine the teachings to substitute one site-specific recombination as taught by Fukushige or the '177 patent with the Int/att system as taught by Griffiths et al. Applicant cites Griffiths for choosing the Cre/lox system of the alteratives available because the recombination is highly sequence-specific, very efficient and occurs at a short target site that is readily incorporated into cloning vectors (Griffiths at column 19, lines 55-59). Therefore, Applicant argues that Griffiths teaches away from such substitutions and that no case of obviousness based on the combined disclosures of Fujushige, Wahl, Lenski and Griffiths has been established.

Response to arguments

Applicant's arguments filed 20 June 2006 have been fully considered but they are not persuasive. Applicant argues that Griffiths makes no indication that one should substitute one recombination system for another, and that the Cre/*lox* system was

chosen specifically for the Griffiths application over the possible alternatives, citing Griffiths at col. 19, ll. 55-59.

The Office notes that Griffiths envisages that the Int/*att* system could be used for sequence transfer between replicons in E. coli, going on to describe this might be achieved in more detail "For example, the donor gene could be flanked by *att* L and *att* R sites such that when Int and Xis proteins are provided in the host cell, recombination between *att* L and *att* R sites would create a circular DNA segment containing the donor gene and a recreated *att* B site. This circular segment could then recombine with an att P site engineered into the recipient plasmid" (col. 19, ll. 37-45).

Thus, this envisaged is full within the boundaries of Griffiths claims 1

"A method of producing recombinant vectors, which method comprises:

causing or allowing recombination between (a) first vectors comprising nucleic acid encoding a population of a first polypeptide chain of a specific binding pair member; and (b) second vectors comprising nucleic acid encoding a population of a second polypeptide chain of a specific binding pair member, at least one of said populations being genetically diverse, the recombination resulting in recombinant vectors each of which comprises nucleic acid encoding a said first polypeptide chain and a said second polypeptide chain, the recombination being promoted by inclusion in said first and second vectors of sequences at which site-specific recombination occurs, each of the first vectors and each of the second vectors including a first site-specific recombination sequence and a second site-specific recombination sequence different from the first, site-specific recombination taking place preferentially between first site-specific recombination sequences on different vectors and between second site-specific recombination sequences on different vectors compared with a first site-specific recombination sequence and a second site-specific recombination sequence on the same vector."

It is therefore apparent that Griffiths suggests an embodiment of the reference invention wherein the Int/*att* system is employed as an alternative to the Cre/*lox* system. In doing so, Griffiths suggests motivation to replace the one recombination system with

the other. As detailed previously it would have been obvious then, to modify the expression vectors taught by Fukushige or the '177 patent, as utilized in host cells. One would have been motivated to make such a modification to obtain the benefit of extending the range of site-specific recombination systems (recombinases and their cognate substrate/recognition sites) as described by Griffiths et al. The rejection is still considered proper and is maintained.

Conclusion

No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Guy Guidry, Ph.D. whose telephone number is 571-272-7928. The examiner can normally be reached on Monday through Friday 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history

information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Guy Guidry, Ph.D.

Examiner

Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER